I.R Iranian Heart Journal; 2016; 17 (1)

## Original Article

# *Evaluation of Diagnostic Characteristics and Predictors of Appropriate ICD Therapy in Patients with Arrhythmogenic Right Ventricular Cardiomyopathy*

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## ABSTRACT

***Background:*** Arrhythmogenic right ventricular cardiomyopathy dysplasia (ARVCD) is a common cause of sudden cardiac death among young adults and athletes. The currents study sought to evaluate clinical characteristics, echocardiographic and ECG diagnostic criteria, and follow-up results in patients with ARVCD.

***Methods:*** In the present case series, the ECG, imaging, and echocardiography records of all patients referring to our tertiary care center between 2000 and 2015 were assessed. Sex, age, cardiovascular risk factors, drug history, and family history of cardiovascular diseases were considered as the study variables. The frequency of all baseline and clinical data and the correlations between those and implantable cardioverter defibrillator (ICD) indication and survival were evaluated.

***Results:*** In this case series, 68 patients with ARVCD (mean age =39.48±15.83 y; 45 male) were evaluated. The most frequent symptom was palpitation, followed by syncope, and the most prevalent ECG findings was T-wave inversion in the precordial leads (P<0.05). Regional RV akinesia or dyskinesia was seen in 77.9%. The ICD was implanted in 55 patients: appropriate and inappropriate therapy was seen in 33 and 12 patients, respectively. The correlation between dyspnea and ICD indication was significant (P<0.05). The relationships between appropriate ICD therapy and dyspnea, peripheral edema, ascites, and severe left ventricular (LV) dysfunction were significant (P<0.05). Multivariate analysis showed that dyspnea and secondary ICD indices were the predictors of appropriate ICD therapy. The mortality rate was 11.8%.

***Conclusions:*** In our patients with ARVCD, the most common symptoms were palpitation, syncope, and T-wave inversion in the precordial leads. The correlations between appropriate ICD therapy and dyspnea, peripheral edema, ascites, and severe LV dysfunction were significant. Dyspnea and secondary ICD indication were the predictors of appropriate ICD therapy. ***(Iranian Heart Journal 2016; 17(1): 20-28)***

**Keywords:** Arrhythmogenic right ventricular cardiomyopathy dysplasia ■ Implantable cardioverter defibrillator ■ Survival

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**Received:** August 30, 2015 **Accepted:** February 20, 2015

Arrhythmogenic right ventricular cardiomyopathy dysplasia (ARVCD), as a common cause of sudden cardiac death among young adults and athletes, is an inherited heart muscle disorder characterized by fibro-fatty infiltration of the right ventricle (RV).[1-4] The manifestation of ARVCD ranges from primarily ventricular tachycardia (VT) to biventricular heart failure, and it may eventually lead to heart transplantation or cardiac death. The prevalence of ARVCD in the general population is approximately 1:1000.[(1-4)] It is usually diagnosed in patients under 40 years of age in at least 80% of the cases.[(5-6)] The Task Force Criteria (TFC) due to the specificity of their association with ARVCD is divided into major and minor criteria, which are based on structural, histological, ECG, arrhythmic, and familial features of the disease.[(7)]

The 2 most common clinical manifestations of ARVCD are arrhythmia and conduction disturbances and history of syncope or dizziness, especially during exercise. Symptoms correlated with heart failure such as dyspnea, edema, and fatigue may occur over time.[(8-9)]Abnormalities of depolarization, conduction, and repolarization secondary to the atrophy of the ventricular walls are seen. T-wave inversion in the anterior precordial leads (beyond $V_1$) in the absence of right bundle branch block (RBBB) is a sensitive finding of ARVCD, which has been seen between 37% and 81% of the cases.[10] Depolarization and elongation of conduction observed in 36% to 76% of the cases in the right precordial leads in the absence of RBBB can be distinguished as the prolongation of the QRS complex (exceeding 110 ms in $V_1$–$V_3$) [(11,12)]. Selective prolongation of the S-wave duration in $V_1$–$V_3$ is seen in 34% to 71% of patients.[(13)] The implantable cardioverter defibrillator (ICD) is an effective method for terminating malignant ventricular tachyarrhythmia. Secondary prevention after survived cardiac arrest or documented sustained VT are the 2 most recommended indications for ICD implantation in ARVCD. ICD therapy as primary prophylaxis in asymptomatic patients must be based on individual risk assessment because of the lack of data supporting this approach. The main indication for primary prophylactic ICD is currently based on either a history of sudden cardiac death at an early age in the family or evidence of extensive RV dysfunction as well as the involvement of the left ventricle (LV). In a cohort of 42 ARVCD patients with the ICD, 78% of the patients experienced at least 1 appropriate discharge during an average of 3.5 years of follow-up.[(14)] Similar findings have been reported by other authors.[(15-17)] The present study evaluated clinical characteristics, echocardiographic and ECG diagnostic criteria, and follow-up results in patients with ARVCD.

## METHODS

In this case series, the clinical characteristics, diagnostic imaging, and ECG criteria in a series of 68 patients with ARVCD from a single referral center in our tertiary care center were assessed. Sex, age, cardiovascular risk factors, any cardiovascular drug consumption and hospitalization history, and family history of cardiovascular diseases were recorded. Additionally, ECG and echocardiographic records of all the patients

were collected. The patients were followed up by telephone in case of incomplete data. The ECG, echocardiographic, magnetic resonance imaging (MRI), and ICD implantation data were evaluated using an individual questionnaire. Survival and its correlation with the study variables were estimated.

### *Statistical Analysis*

The data were analyzed using SPSS, version 20. The categorical data are presented as numbers (%) and the continuous data as means±SDs. The chi-square test or the Fisher exact test was used to compare the categorical variables, and the Student *t*-test was utilized to compare the continuous variables. Correlations between the variables were calculated using the regression test. An $\alpha<0.05$ was considered the level of significance.

## RESULTS

In this study, 68 patients (45 male) at a mean age of 39.48 ±15.83 years were enrolled. The most frequent symptom was palpitation, which was seen in 56 (82%) patients, followed by presyncope in 44 (64%), dyspnea in 33 (48%), peripheral edema in 13 (19%), and ascites in 10 (14%) (Table 1).

**Table 1.** Baseline characteristics and clinical parameters of the study population

| | | N | % |
|---|---|---|---|
| **Dyspnea** | No | 35 | 51 |
| | Yes | 33 | 48 |
| **NYHA class** | NYHA II | 16 | 23.5 |
| | NYHA III | 13 | 19 |
| | NYHA IV | 5 | 7 |
| **Aborted SCD** | Yes | 14 | 21 |
| | No | 54 | 79 |
| **Hypertension** | Yes | 8 | 12 |
| | No | 60 | 88 |
| **Diabetes** | Yes | 5 | 8 |
| | No | 63 | 93 |
| **Hyperlipidemia** | Yes | 13 | 19 |
| | No | 55 | 81 |
| **Smoking** | Yes | 7 | 10 |
| | No | 61 | 90 |

NYHA, New York Heart Association; SCD, Sudden cardiac death

A history of premature sudden cardiac death in a first-degree relative was available in 14 (20%) patients. The most common drugs used were beta-blockers in 40 (58.8%) patients, Class III AAD in 40 (59%), and ACE-I in 32 (48%). Most of the patients (63 [92%]) had baseline sinus rhythm. Baseline QRS in 41 (60%) patients was narrow and was RBBB in 24 (35%). Mean QRS interval in all the leads was 92 msec (in $V_1$–$V_3$ 105 msec and $V_4$–$V_6$ 93 msec), and QT interval was 422 msec. The most prevalent ECG finding was T-wave inversion in the precordial leads (86.8%), which was mostly seen in $V_1$–$V_3$ and beyond. Epsilon wave was seen in 48.5% of the patients; it was found mostly in $V_1$–$V_3$ (30%) as compared with only $V_1$ in 4% and in $V_1$–$V_2$ in 13%. Prolonged S wave (>55 msec) was observed in 50% of the patients, D pattern in 38 patients, and inferior VT axis in 18 patients (Tables 2–4). Moreover, regional RV akinesia or dyskinesia defined on echocardiography was reported in 77.9% of the patients. Out of the 55 patients, the ICD was implanted in 21 (30%) for primary and in 34 (50%) for secondary prevention, which was accompanied by appropriate therapy in 33 patients and with no appropriate therapy in 12 patients. Cumulative ICD therapy was 2.7±1.84 years, time-to-appropriate therapy was 1.37±0.94 years, and time-to-inappropriate therapy was 1.67±1.49 years (Table 5).

The correlations between appropriate ICD therapy and dyspnea, peripheral edema, ascites, and severe LV dysfunction were significant ($P<0.05$). Although the correlation between the severity of dyspnea (NYHA II-IV) and appropriate ICD therapy was not significant, it seems that there was a trend to more therapy with an increase in NYHA class (68% in NYHA II and 84% in NYHA IV; $P=0.26$) (Table 6).

The regression test was used to assess the correlation between symptoms, ICD indication, and echocardiographic variables and showed that the relationship between dyspnea and ICD indication was significant ($P<0.05$). The mean duration of follow-up was 35.06±26.07 months, and the mean time-

to-mortality was 2.37±2.32 years. The mortality rate was 8 (11.8%): 4 patients had cardiac arrhythmia and the other 4 had cardiac failure. Heart transplantation was performed in 3 (4.4%) patients. The correlations between survival and dyspnea, peripheral edema, and ICD indication were significant (P<0.05) (Table 7)

**Table 2.** ECG parameters

| | | N | % |
|---|---|---|---|
| **Baseline rhythm** | SR | 63 | 92 |
| | AFL | 2 | 3 |
| | Paced rhythm | 3 | 4 |
| **QRS morphology** | Narrow | 41 | 60 |
| | RBBB | 24 | 35 |
| | LBBB | 2 | 3 |
| **Epsilon wave** | Yes | 33 | 48.5 |
| | No | 34 | 50 |
| **Epsilon wave leads** | V1 | 3 | 4 |
| | V1+V2 | 9 | 13 |
| | V1+V2+V3 | 21 | 31 |
| **T-wave inversion in precordial leads** | Yes | 58 | 87 |
| | No | 8 | 12 |
| **T-wave inversion leads** | V1 only | 8 | 12 |
| | V1-V2 only | 5 | 7 |
| | V2-V3 only | 1 | 1.5 |
| | V4-V6 only | 1 | 1.5 |
| | V1-V3 and beyond | 44 | 65 |
| **Prolonged S-wave upstroke in $V_1$ through $V_3 \geq$ 55 ms** | Yes | 34 | 50 |
| | No | 33 | 48.5 |
| **VT (ECG, Holter, EST)** | Yes | 46 | 68 |
| | No | 10 | 15 |
| **VT type** | Sustained | 25 | 37 |
| | Nonsustained | 14 | 21 |
| **VT morphology** | LBBB | 38 | 56 |
| | RBBB | 2 | 3 |
| | Indeterminate | 1 | 1.5 |
| **VT axis** | Inferior | 18 | 26.5 |
| | Left or superior | 15 | 22 |
| | Normal | 7 | 10 |
| | Indeterminate | 2 | 3 |
| **Frequent PVCs (> 500/24 h on Holter):** | Yes | 22 | 32 |
| | No | 3 | 4 |
| **Late potential** | Yes | 17 | 25.0 |
| | No | 2 | 3 |
| **Prolonged fQRSd** | Yes | 11 | 16 |
| | No | 8 | 12 |
| **LAS40** | Yes | 6 | 9 |
| | No | 13 | 19 |
| **RMSQ40** | Yes | 9 | 13 |
| | No | 10 | 15 |

SR, Sinus rhythm; LBBB, Left bundle branch block; RBBB, Right bundle branch block; VT, Ventricular tachycardia; PVC, Premature ventricular complex; AFL, Flutter; fQRSd, Filtered QRS duration >114 msec; RMSQ40, Root-mean-square voltage of terminal 40 msec ≤20 μV; LAS40, Duration of terminal QRS ≤40 μV (low-amplitude signal ≥38 msec)

**Table 3**. ECG parameters

| | Mean± SD |
|---|---|
| **QRS width (average in all leads)** | 92.89±24.24 |
| **$V_1$–$V_3$** | 105.71±29.23 |
| **$V_4$–$V_6$** | 93.46±30.43 |
| **$V_1$+$V_2$+$V_3$** | 313.77±72.13 |
| **$V_4$+$V_5$+$V_6$** | 280.22±91.85 |
| **QTc interval** | 423.62±45.65 |

**Table 4**. Echocardiographic and MRI findings

| | | Mean± SD |
|---|---|---|
| **LV ejection fraction** | | 39.8±12.2 |
| **PLAX RVOT** | | 40.1±9.4 |
| **PSAX RVOT** | | 41.1±10.7 |
| **PLAX/BSA** | | 23.1±6.9 |
| **PSAX/BSA** | | 23.4±7.4 |
| **Regional RV akinesia or dyskinesia by echo** | Yes<br>No | 53(78%)<br>14(22%) |
| **RV end-diastolic volume to BSA by MRI** | 125.21 | 44.26 |
| **RV end-systolic volume to BSA by MRI** | 92.79 | 42.41 |
| **RV ejection fraction by MRI** | 25.34 | 9.41 |

MRI, Magnetic resonance imaging; LV, Left ventricle; RV, Right ventricle; RVOT, Right ventricular out flow tract; BSA, Body surface area; PSAX, Parasternal short-axis view; PLAX, Parasternal Long-axis view

**Table 5.** ICD indication and type and mortality rate

| | | | |
|---|---|---|---|
| **ICD indication** | Primary prevention | 21 | 31 |
| | Secondary prevention | 34 | 50 |
| **ICD type** | ICD-VR | 23 | 34 |
| | ICD-DR | 31 | 46 |
| | ICD-CRT | 1 | 1.5 |
| **Appropriate ICD therapy** | Yes-only ATP | 5 | 7 |
| | Yes-shock | 17 | 25 |
| | No | 21 | 30 |
| | Yes-shock and ATP | 11 | 16 |
| **Inappropriate ICD therapy** | Yes-ATP | 2 | 3 |
| | Yes-shock | 10 | 15 |
| | No | 40 | 59 |

ICD, Implantable cardioverter defibrillator; EST, Exercise stress test

P<0.05 was considered the level of significance.

**Table 6.** Correlation between appropriate ICD therapy and variables

| Variables | | Appropriate ICD Therapy | | P value |
|---|---|---|---|---|
| | | No | Yes | |
| **Sex** | Female | 9(39%) | 14(61%) | 0.29 |
| | Male | 12(27%) | 33(73%) | |
| **Palpitation** | Yes | 17(30%) | 39(70%) | 0.84 |
| | No | 4(33%) | 8(67%) | |
| **Dyspnea** | Yes | 6(18%) | 27(82%) | 0.028 |
| | No | 15(43%) | 20(57%) | |
| **NYHA class** | NYHA II | 5(31%) | 11(69%) | 0.26 |
| | NYHA III | 2(14.5%) | 11(85%) | |
| | NYHA IV | 0 | 5(100%) | |
| **Aborted SCD** | No | 3(21%) | 11(79%) | 0.39 |
| | Yes | 18(33%) | 36(67%) | |
| **Peripheral edema** | No | 1(8%) | 12(93%) | 0.044 |
| | Yes | 20(36%) | 35(64%) | |
| **Ascites** | Yes | 0 | 10(100%) | 0.022 |
| | No | 21(31%) | 37(64%) | |
| **Premature SCD in a first-degree relative** | Yes | 5(36%) | 9(64%) | 0.66 |
| | No | 16(30%) | 38(70%) | |
| **ICD indication** | Primary | 12(57%) | 9(43%) | 0.02 |
| | Secondary | 9(26.5%) | 25(73.5%) | |
| **Severe LV dysfunction** | Yes | 5(19%) | 21(81%) | 0.045 |
| | No | 16(39%) | 25(61%) | |
| **VT (ECG, Holter, EST)** | Yes | 13(28%) | 33(72%) | 0.92 |
| | No | 3(30%) | 7(70%) | |
| **Frequent PVCs (> 500/24 h on Holter):** | Yes | 6(27%) | 16(73%) | 0.29 |
| | No | 0 | 3(100%) | |
| **Late potential** | Yes | 5(29%) | 12(71%) | 0.55 |
| | No | 1(50%) | 1(50%) | |
| **Prolonged fQRSd** | Yes | 3(27%) | 8(73%) | 0.63 |
| | No | 3(37.5%) | 5(62.5%) | |
| **LAS40** | Yes | 2(33%) | 4(67%) | 0.91 |
| | No | 4(31%) | 9(69%) | |
| **RMSQ40** | Yes | 3(33%) | 6(67%) | 0.80 |
| | No | 3(30%) | 7(70%) | |

ICD, Implantable cardioverter defibrillator; VT, Ventricular tachyarrhythmia; LV, Left ventricle; SCD, Sudden cardiac death; fQRSd, Filtered QRS duration >114 msec; RMSQ40, Root-mean-square voltage of terminal 40 msec ≤20 μV; LAS40, Duration of terminal QRS ≤40 μV (low-amplitude signal ≥38 msec)
P<0.05 was considered the level of significance.

**Table 7.** Correlations between survival and dyspnea, peripheral edema, and ICD indication

| Means and Medians for Survival Time | | Mean | | Median | | P value |
|---|---|---|---|---|---|---|
| | | 95% Confidence Interval | | 95% Confidence Interval | | |
| | | Lower Bound | Upper Bound | Lower Bound | Upper Bound | |
| Dyspnea | Yes | 70.111 | 100.465 | 19.960 | 76.040 | 0.01 |
| | No | 39.701 | 81.117 | | | |
| Peripheral edema | Yes | 80.658 | 115.913 | 41.677 | 78.323 | 0.04 |
| | No | 54.468 | 86.492 | | | |
| ICD indication | Primary prevention | 25.843 | 49.426 | 17.81 | 62.18 | 0.005 |
| | Secondary prevention | 69.605 | 104.428 | | | |

ICD, Implantable cardioverter defibrillator
P<0.05 was considered the level of significance.

## DISCUSSION

ARVCD manifestation ranges from primary ventricular tachyarrhythmia to biventricular heart failure and may finally lead to heart transplantation or cardiac death. The diagnosis of ARVCD according to the 2010 Task Force Criteria (TFC) is based on 6 categories with major and minor criteria.[18-19]

In the present case series, 68 patients with ARVCD (mean age =39.48 ±15.83 y; 23 female and 45 male) were evaluated. The most frequent symptom was palpitation, followed by syncope, and the most prevalent ECG finding was T-wave inversion in the precordial leads (86.8%). Epsilon wave was seen in 48.5% of the patients. With regard to the recent investigation, the diagnostic features of ARVCD such as epsilon waves and T-wave inversion may disappear on serial ECG evaluations during follow-up.[18] While T-wave inversion in $V_1$–$V_2$ or in $V_4$, $V_5$, or $V_6$ is a minor criterion for ARVCD, epsilon waves constitute a major principle inasmuch as there are rather specific epsilon waves for ARVCD. Precordial T-wave inversion is more sensitive; however, there is a lack of specificity because it is often present in other diseases such as ischemic or congenital heart disease. Likewise, precordial T-wave inversion in $V_1$–$V_3$ and inferior lead T-wave inversion can be observed in a minority of healthy cases.[19] In the current study, regional RV akinesia or dyskinesia was seen in 77.9% of the patients. Data on structural abnormalities in ARVCD mostly arise from the studies in which the patients had a predominant RV phenotype.

In the literature review, abnormalities in the RV in ARVCD have been widely described.[19] Moreover, global drop in RV function, enlargement of the RV, and more subtle regional disease of the RV have been variously described using such different terms as the focal bulges, microaneurysms, segmental dilatation, and regional hypokinesia.

In the present study, the ICD was implanted in 55 patients, comprising 21 patients with primary and 34 patients with secondary prevention: appropriate therapy was seen in 33 patients and inappropriate therapy was observed in 12 patients. The correlation between dyspnea and ICD indication was significant (P<0.05), while the correlation between the severity of dyspnea (NYHA II-IV) and appropriate ICD therapy was not significant (P>0.05). According to our results, it seemed that there was a tendency to ICD therapy with an increase in NYHA class (68% in NYHA II and 84% in NYHA IV; P=0.26). Moreover, the associations between appropriate ICD therapy, peripheral edema, ascites, and severe LV dysfunction were significant (P<0.05). Nevertheless, the correlations between appropriate ICD therapy and echocardiographic and ECG variables were not significant (P>0.05). The correlations between diuretics, spironolactone, and appropriate ICD therapy were significant (P<0.05). ICD implantation for the prevention of sudden cardiac death in patients with ARVDC with documented sustained VT or VF in patients that receive optimal medical therapy and have a reasonable expectation of survival was recommended in the current ACC/AHA/ESC guidelines.[20] Nonetheless, young patients with ARVCD undergoing implantation may be more susceptible to inappropriate ICD therapy with regard to the mean age of the patients of 40.4 years. Inappropriate ICD interventions and ICD-related complications are a significant source of morbidity. Otherwise, patients with ARVCD are often healthy and young individuals. The management of ICD-related adverse events may be challenging and may exert a negative impact on their quality of life.[21-22] Noticeably, the indications, benefits, and risks associated with ICD therapy should be carefully considered and discussed with the patient during the decision-making process before ICD implantation.

In the current study, the mean follow-up duration was 35.06±26.07 months, and the

mean time-to-mortality was 2.37±2.32 years. The mortality rate was 11.8%, and the correlations between survival and dyspnea, peripheral edema, and ICD implantation were significant.

In this retrospective study, the limitations were insufficient patient data, especially ECG and recording at the time of arrhythmia and VT. More prospective studies with larger sample sizes are required to confirm the results reported here. Furthermore, genetic evaluations of patients with ARVCD are required to shed light on the correlations between genetic and clinical presentations, diagnostic methods, and survival of such patients.

## CONCLUSIONS

In our patients with ARVCD, the most common symptoms were palpitation, presyncope, and syncope. Moreover, regional RV akinesia or dyskinesia on echocardiography was present in 77.9% of the patients. The correlations between appropriate ICD therapy and dyspnea, peripheral edema, ascites, and severe LV dysfunction were significant. In the multivariate analysis, dyspnea and secondary ICD indication were the predictors of appropriate ICD therapy.

## ACKNOWLEDGEMENTS

We thank Dr. Mona Heiadarali for assisting with the scientific writing and Dr. Shabnam Madadi for her useful consultation. Also, we thank all the staff of the Electrophysiology Research Center for their great efforts.

**Conflict of Interest:** The authors hereby declare that there is no conflict of interest.

**Funding Support:** This project was financially supported by the fund of Iran University of Medical Sciences.

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